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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,160	08/09/2001	Sushma Pati	A-64580-4/RFT/RMS/AMS	4009

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/927,160	**Applicant(s)** PATI ET AL.	
	Examiner Anne-Marie Falk, Ph.D.	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 November 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *03 November 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *32-34,36,37 and 41-70*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

Anne-Marie Falk, Ph.D.
Primary Examiner
Art Unit: 1632

Continuation Sheet (PTOL-303)

Continuation of 5. Applicant's reply has overcome the following rejection(s):

The amendments to Claims 32 and 63 overcomes the rejection of Claims 32-34, 36, 37, and 41-70 under 35 U.S.C. 101.

Continuation of 11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because:

At page 7 of the response, Applicants characterize the rejection under 35 U.S.C. 112, first paragraph as "three separate scope of enablement rejections." On the contrary, no scope of enablement has been indicated and therefore the rejection cannot be characterized as a scope of enablement rejection.

At page 8 of the response, Applicants state that "[t]he Examiner appears to concede that the specification *does* in fact teach how to make the recited transgenic mammals" (emphasis original), referring to page 8 of the Office Action. Applicants refer specifically to the Examiner's statement, responding to Applicants arguments regarding the Maga et al. (2003) reference, that "the enablement requirement is not satisfied by addressing only the how to make prong of the enablement requirement because the specification must also teach how to use the claimed invention. A method of making has use only if the product made has a use and one of skill in the art would know how to use the product made." It can hardly be said that such a statement concedes that the specification teaches how to make the recited transgenic mammals, particularly in view of the fact that the Examiner has stated that only mice with a single point mutation in the gene encoding ornithine carbamoyltransferase have been prepared. Likewise, Applicants' statement at page 11, paragraph 3 of the response, is incorrect. The Examiner has not acknowledged that the specification teaches how to make the recited transgenic mammals using the claimed methods.

At pages 7-12 of the response, Applicants assert that the broad method can generally be applied to create a variety of different types of genetic modifications. At page 9, paragraph 2 of the response, Applicants assert that "the claims are generic to, and read on, any user-desired phenotype." Notably missing from Applicants' response is any acknowledgement that the **elected** invention is drawn to a method of making a transgenic mammal comprising a modified endogenous nucleic acid, wherein the preselected target DNA sequence encodes an **enzyme** and where the claims recite an insertion sequence, the **elected** species is a gene encoding a **human enzyme.** See page 7, lines 6-9 of the Office Action of May 3, 2005. It can hardly be said that "the claims are **generic to**, and read on, **any user-desired phenotype**" (emphasis added) when the claims are specific to disrupting an α-galactosyl transferase gene by an insertion sequence (Claim 56). This claim reads on the elected invention, and further reads on the elected species where the insertion sequence is a human enzyme. It can hardly be said that any user-desired phenotype can be obtained by this genetic modification, even given the very large scope of human enzyme genes that could be inserted into the pig, goat, cow, mouse, rat, etc. α-galactosyl transferase locus. Given that the claims are directed to very **specific genetic modifications**, Applicants' arguments that the transgenic mammals produced by the claimed methods "have many possible uses" are not persuasive. The art of record establishes that the phenotype produced by any specific genetic modification is unpredictable. Thus, it is the function of the specification to teach a specific use for the wide variety of animals (mouse, goat, rat, pig, primate, cow, etc.) with the specific genetic modifications claimed. As pointed out in the prior Office Action, a method of making has use only if the product made has a use and one of skill in the art would know how to use the product made. See page 8, paragraph 1 of the Office Action of May 3, 2005. The specific use of the animal is dependent upon the phenotype exhibited upon genetic modification of the animal. Applicants' arguments are not directed to the elected

invention, but rather are directed to Claims 32-34 and 36 exclusively, which are broadly drawn to any genetic modification. The elected invention, however, is drawn to specific genetic modifications. At page 11, paragraph 2 of the response, Applicants state that "the methods claimed in the instant application are **generic** methods that can be used to produce transgenic mammals having **any desired genotypic alteration**" (emphasis added). How can a method that involves disrupting an α-galactosyl transferase gene (Claim 54) be a generic method "that can be used to produce transgenic mammals having any desired genotypic alteration"? Suffice it to say that the elected invention is the one being examined and the elected invention is in no way a generic method "that can be used to produce transgenic mammals having any desired genotypic alteration."

Thus, the rejection under 35 U.S.C. 112, first paragraph is maintained, for reasons of record.

At pages 11-12 of the response, Applicants assert that "targeted endogenous DNA sequence" is defined in the specification as "polynucleotide sequences contained in a target cell," at page 22, lines 28-29. This does not address the claim language at issue. The indefinite claim language recites "modified endogenous nucleic acid." The rejection states that it is unclear relative to what standard or point of reference the endogenous nucleic acid is considered to be "modified." Applicants assert that it would be clear to one of ordinary skill in the art that the nucleic acid is modified compared to the original sequence present in the target cell to be modified. However, there is nothing in the specification that defines the modification as being a difference as compared to the original sequence in the **target cell**. Furthermore, Applicants state that the specification defines the types of sequences regarded as "endogenous" to include "genes originally derived from an exogenous source such as a virus," referring to the specification at page 22, line 28 to page 23, line 18. However, the language in the specification is non-limiting and, although

providing a few examples of what is intended to be included in the terminology, the specification does not provide an actual definition.

Thus, the rejection under 35 U.S.C. 112, second paragraph is maintained, for reasons of record.